Stochastic Models for Single Neuron Firing Trains: A Survey

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Summary

The spontaneous firing activity of single neurons can be viewed in the framework of stochastic modelling. Of special interest in this regard is the point process defined by the times at which neuronal discharges occur. In this paper, point process models for the spike (discharge) train of spontaneous active neurons are considered. The main physiological features included in most of these models are excitation, inhibition, temporal summation, and decay. Since all the point processes considered are stationary, interest is focussed on the interspike interval distribution associated with each model.

1. Introduction

The nervous systems of higher organisms are, in effect, communication systems transmitting electro-chemical impulses (or signals). The structural unit of these communication systems is the individual nerve cell or neuron. Although neurons are highly diversified in both structure and function, each neuron is made up of the same basic parts: the soma, the axon, the dendrites and the synapses. Figure 1 shows a reconstructed motor neuron. Below we give a highly oversimplified discussion of the physiological properties of the typical neuron.

Figure 1 goes about here

Each neuron receives signals from many other neurons through terminal contacts or synapses, which are found on the neuron's cell body or soma, and on its dendrites, the tree-like structures which are rooted in the soma. The geometry of the dendritic trees varies greatly, and is often crucial to the neuron's function. At the soma the signals, received via the synaptic connections on the soma and the dendrites, are combined or integrated. In the motor neuron this integrative region is located near the axon hillock, where the soma and axon are joined. When the level of excitation at the axon hillock reaches a threshold level, the neuron fires, transmitting an output signal (action potential, discharge or spike) down the axon to connecting neurons. These discharges may be treated as forming a stochastic point process (see Stein, 1972, for discussion of this point), and the topic of this paper is the modelling of this process.

The neuron consists of a well-conducting electrolyte gel, surrounded by an insulating membrane. Changes in the permeability of the membrane and in the ionic concentration of the interior and exterior of the cell lead to

the action potential referred to above (see Katz, 1966). The details of this electro-chemical process need not concern us here, but it is important for us to note that when a neuron emits an action potential it becomes temporarily incapable of integrating further input signals. For a brief period of one or two milliseconds the neuron does not respond to any stimulus (the absolute refractory period), and for several seconds thereafter its relative threshold (i.e. the total amount of excitation required to trigger an action potential) is higher than usual (relative refractory period). These refractory periods are not fixed, and for our purposes can be thought of as random variables.

Viewed in terms of electrical circuits, the neuron is not a perfect integration of input signals over indefinite periods of time. The inputs leak away roughly exponentially with time (Stein, 1972), and this decay of the cell membrane toward its resting potential is an important factor to be considered in the modelling process.

In the following sections we focus on the spontaneous firing activity of single neurons, and we discuss various stochastic models for the neuron firing process. In each case we derive expressions for the distribution of time intervals between successive firings of the neuron (interspike intervals). The firings are treated as instantaneous and indistinguishable so that our data consist of the times of spike occurrences, $t_1, t_2, \ldots$, or, equivalently, of the lengths of successive interspike intervals. The process is stochastic due to random variations inherent in the inputs, and it is a point process by virtue of the instantaneity and indistinguishability of the firings (Moore, Perkel and Segundo, 1966; Perkel, Gerstein and Moore, 1967a). Moreover we assume the stochastic process to be stationary, i.e. the process does not

change over time. Thus it makes sense to examine the interspike interval distribution. For several of the models considered below, much effort has gone into proofs of stationarity, and where suitable we give references to this work.

When the interspike intervals are drawn independently from a common probability distribution, the stochastic process is a renewal process (see Cox, 1962), and the entire process is fully characterized by the interspike interval distribution. When the discharge process is stationary but not a renewal process, other characteristics of the process are of interest, such as the correlation between contiguous and non-contiguous interspike intervals. We shall not examine such characteristics in detail, but we do provide the reader with references where such characteristics are considered. A special class of these renewal models is characterized by the use of a Brownian motion-like theory, and in the following section we deal with these models.

As we pointed out above, in this survey we focus on the spontaneous electro-chemical activity of single neurons, and the resulting train of firings. Another topic of great interest among physiologists is the firing pattern which results when the neuron is subjected to specific modes of electro-chemical stimulation. The related stochastic modelling problems are considerably more complex than those considered here, and as yet they have received little attention from applied probabilists.

While the modelling of single neuron discharge activity leads to interesting applied probability problems, from a physiological viewpoint such modelling is only of interest as the first step in the study of the activity generated by interconnected aggregates of nerve cells, often referred to as neural networks or neural nets. Cowan (1970) has used the method of statistical mechanics to study interconnected aggregates of simplified model neurons (see Figure 2 for an illustration of the type of aggregate studied by Cowan).

Considerably more work on models for sets of interconnected neurons is required. The recent developments in the areas of Markov renewal processes (e.g. see Çinlar, 1969) and multidimensional point processes (e.g. see Cox and Lewis, 1972) may be of help in this regard. Hopefully, as a start, probabilistic models for a pair of interconnected neurons could be used to account for physiological observations of the sort reported in Perkel, Gerstein and Moore (1967b), and in Moore et al. (1970) on cross-correlegrams.

Figure 2 goes about here

A further aspect of neural modelling, which we do not consider in this review, attempts to characterize discharge trains considered to arise from the pooling or superposition of several component processes (see Ten Hoopen and Reuver, 1966; Ten Hoopen, 1967; Sabah and Murphy, 1971). For a review of recent results in the area of the superposition of point process see Çinlar (1972).

In this survey we have tried to consider all of the literature on probabilistic models for single neuron discharge. Papers on this topic have occurred in a wide variety of journals and in several languages, and there are likely to be many papers and possibly models which we have missed. In particular, we recognize that we have not included any references to the extensive neurophysiology literature in the Russian language.

Several papers related to the stochastic modelling of spontaneous neural activity do not quite fit within the framework we have chosen for the classification of probabilistic models. We include these papers in the reference list for completeness.

2. Diffusion Models

If the number of synaptic inputs to a neuron is large, if the inputs are relatively independent, and if the electro-chemical effect of each input is small relative to the neuron's threshold, the level of exictation recorded in the soma can be viewed as being analogous to the position of a particle undergoing a random walk with the threshold being analogous to the position of a barrier for the particle. Gerstein and Mandelbrot (1964) first suggested such a random walk model, and they treated the special model which integrates inputs without loss (i.e. decay) up to threshold. Other authors have built on this model, allowing for the exponential decay of the inputs (Stein, 1965, 1967; Gluss, 1967; Bayley, 1968; Johannesma, 1968, 1969; Roy and Smith, 1969; Fienberg, 1970). Rather than using exponential decay, Ten Hoopen (1966a) gives input signals a life-time governed by a Poisson process.

Following Johannesma (1968) and Fienberg (1970) we can describe the diffusion model with decay as follows:

(a) The state of the neuron is characterized at any point in time by level post-synaptic potential (P.S.P.) or integrated level of electrical activity, $X(t)$. At time zero, $X(0) = x_0$.

(b) There are two independent input processes, one excitatory and one inhibitory. The neuron receives excitatory pulses of magnitude ϵ according to a Poisson process (see Cox and Miller, 1965) with parameter α, and inhibitory pulses of magnitude $-\epsilon$ according to a Poisson process with parameter β.

(c) The P.S.P., $X(t)$, is subject to exponential decay with time constant τ, to a resting level x_r.

(d) When $X(t)$ reaches a fixed threshold level S an output pulse or firing occurs and the potential is reset to x_0.

The fact that in (b) the excitatory and inhibitory pulses are of the same magnitude leads to no loss of generality due to adjustments that can be made to the parameters α and β in the diffusion approximation equation.

Now if we let $f = f(t,x) = f(t,x,x_0)$ be the probability density function for the membrane to be at potential level x at time t given that $X(0) = x_0$, and $F(t,x,x_0)$ the corresponding cumulative distribution function, we can derive the following equation for the potential at time $t+\delta t$:

$$\begin{aligned} F(t+\delta t,x) = {} & F(t,\{x-x_r\}e^{\delta t/\tau} + x_r)[1 - (\alpha+\beta)\epsilon\cdot\delta t] \\ & + F(t,\{x-x_r-\epsilon\}e^{\delta t/\tau} + x_r)\alpha\cdot\delta t \\ & + F(t,\{x-x_r+\epsilon\}e^{\delta t/\tau} + x_r)\beta\cdot\delta t + o(\delta t). \end{aligned} \qquad (2\text{-}1)$$

According to the Poisson process for inputs the probability of an excitatory input in $(t,t+\delta t)$ is $\alpha\cdot\delta t + o(\delta t)$, the probability of an inhibitory input is $\beta\cdot\delta t + o(\delta t)$, and the probability of more than one input is $o(\delta t)$. Thus the first term on the right hand side of (2-1) gives the probability of being at a level of at most $\{x-x_r\}e^{\delta t/\tau} + x_r$ at time t, times the probability of no impulses in $(t,t+\delta t)$. The second terms give the probability of being at a level of at most $\{x-x_r-\epsilon\}e^{\delta t/\tau} + x_r$ and at a level of at most $\{x-x_r+\epsilon\}e^{\delta t/\tau} + x_r$ respectively at time t, times the probability of an excitatory or inhibitory pulse in $(t,t+\delta t)$. Using Taylor series expansions for F about x (considering terms of order δt or greater), restricting ϵ to be small relative to $S-x_r$ and $S-x_0$, and then letting $\delta t \to 0$, we end up with the following equation for f:

$$\frac{\partial f(t,x)}{\partial t} = \frac{\epsilon^2}{2}(\alpha+\beta)\frac{\partial^2 f(t,x)}{\partial x^2} - \frac{\partial}{\partial x}\left\{\left[\epsilon(\alpha-\beta) - \frac{x-x_r}{\tau}\right]f(t,x)\right\}. \qquad (2\text{-}2)$$

This is the familiar diffusion or Fokker-Plank equation, and is the forward equation of the Ornstein-Uhlenbeck process (Feller, 1971), which also appears in the study of population genetics (Kimura, 1964; Ewens, 1969).

Johannesma (1968) and Roy and Smith (1969) each give a lengthy discussion of the distribution of first passage time through a fixed threshold, S. In both cases, the discussion is complicated because the authors first attempted to find expressions for the Laplace transform of the first passage time distribution, and then the mean and variance of this first passage time distribution from the Laplace transform. Johannesma also shows how to derive all the moments of the distribution. Sugiyama, Moore, and Perkel (1970) derive the Laplace transform of the first-passage time distribution in a different form using parabolic cylindrical functions.

Geisler and Goldberg (1966) and Roy and Smith (1969) have suggested neural models with threshold values $S = S(t)$, which vary with time, decaying exponentially to some asymptotic level S_0. First passage time problems with such thresholds are considerably more difficult to handle than those with fixed thresholds. Eysel (1971) suggests the use of a hyperbolic threshold.

Siebert (1969) and Sugiyama, Moore and Perkel (1970) solved the first passage time problem for the special case where the threshold is

$$S = x_r + \tau\epsilon(\alpha-\beta). \tag{2-3}$$

The first passage time distribution is then

$$p(t) = \frac{(S - x_0)(2/\tau)^{3/2}}{(2\pi)^{\frac{1}{2}}\epsilon^2(\alpha+\beta)} [\exp(2t/\tau) - 1]^{-3/2} \times \exp(2t/\tau)\exp\left(- \frac{(S - x_0)^2}{\epsilon^2(\alpha+\beta)[\exp(2t/\tau) - 1]}\right). \tag{2-4}$$

In this case the mean firing time is always finite, and the typical interval distribution is unimodal.

Recently, Cowan (1971), in a study of more general first-passage time distributions, has shown that closed form solutions for the threshold situations described above do not exist. He has also been exploring ways to approximate the solutions. Sugiyama, Moore and Perkel (1970) suggest a different approximation for the fixed threshold problem using finite difference equation techniques. Again, they find the typical interval distribution to be unimodal.

Before concluding this section we note the related work on the diffusion approximation and first-passage time problems by Capocelli and Ricciardi (1971, 1972), and the birth and death process models of Goel, Richter-Dyn and Clay (1972) which result in diffusion-like equations, with similar first passage time problems.

3. Gating Models and Models with Clustered Firings

Smith and Smith (1965), in studies of spontaneous firing of cortical neurons in the unanesthetized isolated forebrain of the cat, found inter-spike interval distributions which appeared to be mixtures of two exponential components segregated in time. To account for such discharge distributions they proposed the following model:

(1) excitation arrives at the neuron according to a Poisson process with parameter C;

(2) the neuron has periods of inactivity (off-periods) during which excitatory stimuli do not register, and periods of hyperactivity (on-periods) during which each excitatory stimulus causes the neuron to discharge;

(3) each new on-period of activity initiates a discharge;

(4) the duration of an on-period is exponentially distributed with parameter B;

(5) the duration of an off-period is exponentially distributed with parameter A;

(6) the random variables in (1), (4) and (5) are mutually independent.

Note how the Poisson "shower" in (1) is gated off and on (see Figure 3). The "shower" produces a high frequency Poisson component in the output process, and the discharges at the beginning of each on-period produce a low frequency Poisson component.

Figures 3 and 4 go about here

We start the process with the initiation of an on-period (and thus there is a discharge at time 0). There are two mutually exclusive ways in which the next discharge can occur. The probability that the second discharge occurs in $(t, t+\delta t)$ with no intervening off-period equals

$$Ce^{-Ct}(e^{-Bt})\delta t. \qquad (3\text{-}1)$$

The probability that the Poisson shower is gated off in (0,t) before the next discharge, and then the second discharge occurs in (t,t+δt) coincident with the start of a new on-period is

$$[\int_0^t Be^{-(B+C)u}Ae^{-A(t-u)}du]\delta t. \qquad (3\text{-}2)$$

Combining these two expressions (and after a little algebraic manipulation) we get the interspike interval distribution p.d.f. as

$$p(t) = \frac{B}{B+C-A}Ae^{-At} + \frac{C-A}{B+C-A}(B+C)e^{-(B+C)t}, \qquad (3\text{-}3)$$

which is a mixture of two exponential distributions (provided $C > A$), and thus coincides with the desired result of Smith and Smith. Moreover, the discharges form a renewal process themselves. We can get a similar mixture of exponentials by having an on-period end rather than start with a discharge.

The gating model just described does not include inhibitory stimuli as such, but we can interpret the off-periods as periods of intense inhibitory stimulation, or as dead-time periods which follow inhibitory arrivals that have sufficient power to desensitize the neuron to the ongoing excitatory Poisson shower.

Thomas (1966) proposed a second model to account for the experimental observations of Smith and Smith:

(1′) There is a main Poisson process (with parameter α), controlled by mechanisms external to the neuron, which produces discharges.

(2′) Following each main discharge, there is an "after-potential," V_x, which results from the two ends of the neuron recovering from the discharge at different rates. The V_x's are i.i.d. random variables; and a subsidiary process begins if $V_x \geq \theta$, a threshold value.

(3′) The probability of a subsidiary process starting is $r = V_r\{V_x \geq \theta\}$.

(4′) The subsidiary process generates an "after-burst" or a series of subsidiary discharges. The first subsidiary discharge occurs at time y_0 after the start of the subsidiary process, and is followed by an after-potential, V_y, which leads to another discharge at time y_0+y after the start if $V_y \geq \theta$, etc. We assume that the V_y's are identically distributed random variables, independent of each other and of the V_x's. Thus the y's and y_0 are independent random variables, which we assume to have a common exponential distribution with parameter β. Moreover, we let $p = P_r\{V_y \geq \theta\}$.

(5′) A main discharge terminates any current subsidiary process, but starts a new one according to the mechanism of (2′) with probability r.

The point process describing the succession of discharges for this model is stationary; however, it is not a renewal process. The inter-spike interval p.d.f. for the Thomas model is

$$\frac{\beta(1-p) + \alpha(1-r)}{\beta + \alpha + \beta(r-p)} \alpha e^{-\alpha t} + \frac{r(\beta+\alpha)}{\beta + \alpha + \beta(r-p)} (\alpha+\beta) e^{-(\alpha+\beta)t}, \qquad (3\text{-}4)$$

which is a mixture of exponentials, and thus can account for the observed data of Smith and Smith. The derivation of (3-4) is somewhat complicated and we refer the interested reader to Thomas (1966) for details. Ekholm and Hyvärinen (1970), and Ekholm (1972), also describe a two-state, two-interval semi-Markov process similar to the one corresponding to Thomas' model.

Reuver and Ten Hoopen (1972) describe two "threshold" models to account for the experimental data of Smith and Smith, and more generally for clustered firing of neurons. The models which they fit to the Smith and Smith data are in effect mixtures of eight and ten exponential components; however, the p.d.f.'s

can be approximated by a simple mixture of two exponentials. In addition, Hochman (1971) has shown that a threshold model, developed in Hochman and Fienberg (1971) and described here in Section 6, produces an interspike interval p.d.f. which is almost identical to (3-3).

Hochman (1971) has generalized the Smith and Smith model in a way that the gate can be in n different states during each of which inputs occur at a state-dependent rate. For n = 2, his model has the effect of allowing discharges in the off-period of Smith and Smith, but at a different Poisson rate than those in the on-period, say D. In addition, a change in the gate state does not cause a discharge. In this case the discharges form a renewal process, and the interspike interval distribution is once more a mixture of two exponentials, whose transformed p.d.f. is

$$p^*(s) = \frac{[(AC^2 + BD^2)/(AC + BD)]s + (AC + BD + DC)}{s^2 + (A + B + C + D)s + (AC + BD + DC)} . \qquad (3\text{-}5)$$

4. Selective-Interaction Models

Many physiologists have reported experimental data showing that the distribution of interspike intervals is, in some cases, multimodal in nature. Ten Hoopen and Reuver (1965a) proposed the following model to describe this phenomena:

(a) the input to the neuron consists of stimuli generated by two independent renewal processes, one excitatory and the other inhibitory, with probability density functions $\varphi(t)$ and $\psi(t)$, respectively;

(b) whenever one or more inhibitory stimuli occur, the next excitatory stimulus is eliminated;

(c) every excitatory stimulus produces a neuronal discharge, provided that it is not deleted by a preceding inhibitory stimulus.

This model was suggested by the work of Bishop, Levick and Williams (1964), and its workings are illustrated in Figure 5.

Figure 5 goes about here

Ten Hoopen and Reuver studied two basic versions of this selective-interaction model. In the first of these, Model A, the excitatory process is arbitrary with p.d.f. $\varphi(t)$, and is inhibited by Poisson process with parameter μ. Starting at time 0, there are two ways in which the first discharge can occur in $(t, t+\delta t)$: either the first excitatory stimulus arrives at time t and there are no intervening inhibitory arrivals, or the first arrival of an excitatory stimulus is at time $y < t$, and this is preceded by the arrival of an inhibitory impulse. If we let $p(t)$ be the p.d.f. of the first-passage or interspike interval distribution (they are the same in this case because the inhibitory process has no memory), we have

$$p(t) = \varphi(t)e^{-\mu t} + \int_0^t [\varphi(y)(1-e^{-\mu y})]p(t-y)dy. \qquad (4\text{-}1)$$

Denoting the Laplace transform of the function f(t) by f*(s), and taking Laplace transforms of both sides of (3-1), we get

$$p^*(s) = \varphi^*(s+\mu)/[1 + \varphi^*(s+\mu) - \varphi^*(s)]. \tag{4-2}$$

When $\varphi(t)$ is a gamma density, i.e.

$$\varphi(t) = \frac{\lambda(\lambda t)^{k-1} e^{-\lambda t}}{\Gamma(k)}, \quad k \geq 1, \tag{4-3}$$

we can think of our model for the neuron as acting in two stages. First, excitatory inputs arrive at an integrator according to a Poisson process with parameter λ. After the arrival of k excitatory stimuli, an integrated excitatory stimulus is released to a second processing unit where it is allowed to interact with inhibitory stimuli.

Figure 6 goes about here

For $k \geq 20$, Bishop et al (1964), Ten Hoopen and Reuver (1965a), and Ten Hoopen (1966b) found that p(t) will be multimodal with significant troughs between the modes. Dietz (1968) has studied similar models which produce multimodal interval distributions. As Hochman (1971) points out, the first mode is due to the undeleted first occurrences of the integrated excitatory process, the second mode to deleted first occurrences followed by undeleted second occurrences, and so on. Using this argument we see that the nth mode occurs at

$$t_n = [n(k+1) - 1]/\lambda, \quad \text{for } n = 1,2,\ldots, \tag{4-4}$$

and that the modes become progressively less distinct, eventually disappearing. Note that t_n does not depend on μ. The mean interspike interval,

$$\bar{t} = \left(\frac{k}{\lambda}\right)\left(1 + \frac{\mu}{\lambda}\right)^k, \tag{4-5}$$

however, does depend on μ, as does the variance (see Coleman and Gastwirth, 1969)

$$\sigma^2 = \frac{k}{\lambda^2}\left(1+\frac{\mu}{\lambda}\right)^k\left[k+1+k\left(1+\frac{\mu}{\lambda}\right)^k - \frac{2k\lambda}{\mu+\lambda}\right]. \qquad (4\text{-}6)$$

Coleman and Gastwirth also consider the case where $\varphi(t)$ is a finite mixture of exponentials, and they present general formulae for the mean and variance of the interspike interval distribution for arbitrary $\varphi(t)$.

The second version of the selective-interaction model studied by Ten Hoopen and Reuver (Model B) has an excitatory process which is Poisson with parameter λ, that is inhibited by an arbitrary process with p.d.f. $\psi(t)$. In this case, the discharges do not form a renewal process since the time of the next spike depends on the occurrence of the previous inhibitory arrival, unless $\psi(t)$ is an exponential density function. If we now let p(t) be the p.d.f. for the interspike interval distribution, then its Laplace transform (L.T.) is given by

$$p^*(s) = \frac{\lambda}{\lambda+s} + \frac{\lambda^2}{C(\lambda+s)^3}D(s), \qquad (4\text{-}7)$$

where

$$D(s) = [1-\psi^*(s+\lambda)]\frac{s[\psi^*(\lambda)-1] - \lambda[\psi^*(s+\lambda)-\psi^*(\lambda)]}{1-\psi^*(s+\lambda)+\lambda\psi^{*\prime}(s+\lambda)}, \qquad (4\text{-}8)$$

and

$$C = \lambda\int_0^\infty t\psi(t)dt - \{1-\psi^*(\lambda)\}. \qquad (4\text{-}9)$$

Ten Hoopen and Reuver's derivation of (4-7) is quite complicated, but Lawrance (1970b, 1971) gives two alternative derivations, the second of which is quite straightforward.

As we remarked above, the discharge or spike process for Model B is not a renewal process. Lawrance (1970a, 1970b) shows that, if the process begins with a certain set of equilibrium conditions, the discharge process is simple stationary, in that the distribution of discharges over a single interval

is invariant under shifts away from the origin. Thus it makes sense to speak about the interspike interval distribution whose transform is given by (4-7). Lawrance (1970b) also gives the L.T.'s of three point processes which are related to the discharge process:

(a) the process of deleted excitatory stimuli,

$$\frac{\lambda^2[\psi^*(s) - \psi^*(\lambda)]}{(\lambda^2 - s^2)[1 - \psi^*(\lambda)]}, \tag{4-10}$$

(b) the process of inhibitory stimuli which cause a deletion, i.e. which are followed by an excitatory stimuli,

$$\frac{\psi^*(s) - \psi^*(s + \lambda)}{1 - \psi^*(s + \lambda)}, \tag{4-11}$$

(c) the process of inhibitory stimuli which do not cause a deletion, i.e. which are followed by additional inhibitory stimuli,

$$\frac{\psi^*(s + \mu)}{1 + \psi^*(s + \mu) - \psi^*(s)}. \tag{4-12}$$

Expression (4-12) is the same as (4-2) except that the roles of the excitatory and inhibitory stimuli have been reversed. Similarly (4-10) and (4-11) give the transformed distributions of inactive and active inhibitory stimuli, respectively, for the reversed process.

Using first the equilibrium initial conditions referred to above and then a different "average-event" set of initial conditions, Lawrance (1971) derives the joint distribution of pairs of contiguous interspike intervals, and he gives expressions relating the two joint distributions. For the average event initial conditions he also gives the joint distribution of non-contiguous interspike intervals.

Ten Hoopen and Reuver (1967a) and Srinivasan and Rajamannar (1970a) treat the more general selective-interaction model with arbitrary excitatory and inhibitory renewal processes. Lawrance (1970a) generalizes these results by allowing the excitatory process to be any general stationary point process.

Basawa (1971), on the other hand, considers the interaction of two independent Markovian point processes. He focuses on a pure birth process inhibited by either a Poisson or a pure birth process, and a stationary Markov process inhibited by a Poisson process (the latter being a special case of Lawrance's work). None of these generalizations seem to be of direct use in neural modelling.

Yet other authors have introduced modifications to the Ten Hoopen-Reuver selective-interaction model. Coleman and Gastwirth (1969) allow the effect of the inhibitory stimuli to decay (or be extended) over time. In their first model, $\varphi(t)$ is arbitrary, $\psi(t)$ is exponential with parameter μ, and "one or more inhibitors will eliminate the next (excitatory) stimulus arriving within a time T" where T is a constant. This leads to an interspike interval density whose L.T. is

$$p^*(s) = q^*(s)/[1 + q^*(s) - \varphi^*(s)] \tag{4-13}$$

where $q^*(s)$ is the L.T. of

$$q(t) = \varphi(t)e^{-\mu \min(t,T)}. \tag{4-14}$$

The second model of Coleman and Gastwirth allows T to be a positive random variable with distribution function, H(t), and the L.T. of the interspike interval density becomes

$$\lambda(\lambda+s)\left\{\lambda(\lambda+s) + s\left[\int_0^\infty \exp\{-(\lambda+s)t\} \times \exp\left(-\mu\int_0^t [1 - H(x)]dx\right)dt\right]^{-1}\right\}^{-1}. \tag{4-15}$$

The third model of Coleman and Gastwirth allows an inhibitory stimulus to eliminate all subsequent excitatory stimuli arriving within a time T. Thus there is a dead-time period following each inhibitory stimulus which can be determined in one of two ways:

(a) the dead period is that of a Type II counter (see Takács, 1962), with each inhibitory stimulus being effective for its (possible) random lifetime;

(b) the arrival of an inhibitory stimulus wipes out the remaining effect of any preceding ones, and the dead period ends if the lifetime of an inhibitory stimulus ends before the arrival of another one.

Letting $\varphi(t)$ be exponential with parameter λ, we get the following transformed interspike interval p.d.f.'s:

$$\text{(a)} \qquad p^*(s) = \left\{1 + \gamma\, e^{\mu/\gamma} \left(\frac{\mu}{\gamma}\right)^{s/\gamma} \left[\lambda \int_0^{\mu/\gamma} x^{s/\gamma - 1} e^{-x}\, dx\right]^{-1}\right\}^{-1} \tag{4-16}$$

where $h(t) = H'(t)$ is exponential with parameter γ, and

$$\text{(b)} \qquad p^*(s) = \frac{\lambda}{\lambda + \mu + s - \mu(s+\mu)h^*(s+\mu)/[s + \mu h^*(s+\mu)]} \,. \tag{4-17}$$

The expression for case (b) given by Coleman and Gastwirth is incorrect, and (4-17) was derived by Hochman (1971). Srinivasan and Rajamannar (1971) consider a more general version of case (a).

Finally, Råde (1972) modifies the selective-interaction model so that one or more stimuli from the inhibitory process eliminate the next k stimuli of the excitatory process with probability p_k, where $\sum_{k=0}^{\infty} p_k = 1$. The selective-interaction model is characterized by $p_1 = 1$. In the case where the inhibitory process has an exponential density with parameter μ, the firings form a renewal process whose transformed density is

$$p^*(s) = \frac{p_0\varphi^*(s) + (1 - p_0)\varphi^*(s+\lambda)}{1 - [\varphi^*(s) - \varphi^*(s+\lambda)]\left[\sum_{k=0}^{\infty} p_k \{\varphi^*(s)\}^{k-1}\right]} \,. \tag{4-18}$$

Note that letting $p_1 = 1$ reduces (4-18) to (4-2).

The main drawback of the selective-interaction models is that they ignore the temporal and spatial summation of excitation that is considered physiologically necessary to produce neuronal discharges. We consider models which incorporate the summation of excitation up to some threshold value in Section 6.

5. Feedback and Feedforward Inhibition Models

In Section 4 we considered neural models based on selective interaction of independent renewal processes for excitation and inhibition. Now we turn to models where the two processes are dependent, triggering one another according to certain mechanisms.

We continue to consider an excitatory renewal process with an interval p.d.f. $\varphi(t)$, and an inhibitory renewal process with interval p.d.f. $\psi(t)$. One or more inhibitory stimuli delete the next excitatory stimulus, and undeleted excitatory stimuli yield discharges. In Model I, suggested by Ten Hoopen and Reuver (1968), every excitatory stimulus (deleted or not) triggers a new inhibitory renewal sequence with interarrival density $\psi(t)$, which continues until the next excitatory stimulus (deleted or not). Here inhibition is being fed forward, since all incoming excitatory stimuli exert inhibitory action. When $\psi(t)$ is an exponential density the model coincides with the Ten Hoopen-Reuver selective-interaction model of Section 4. Ten Hoopen and Reuver (1968) give general expressions for the interspike interval density. Srinivasan and Rajamannar (1970b) simplify these results, giving the transformed density as

$$p^*(s) = \frac{k^*(s)}{1 - k^*(s) - \varphi^*(s)} \tag{5-1}$$

where

$$k(t) = \varphi(t)[1 - \int_0^t \psi(u)du]. \tag{5-2}$$

When $\varphi(t) = \lambda \exp(\lambda t)$, (5-1) reduces to

$$p^*(s) = \frac{\lambda[1 - \psi^*(s+\lambda)]}{s + \lambda - \lambda\psi^*(s+\lambda)} . \tag{5-3}$$

Model II of Ten Hoopen and Reuver is similar to Model I except that only undeleted excitatory stimuli trigger a new inhibitory renewal sequence. Thus the neuron itself triggers inhibition activity via its discharges so that we

have feedback inhibition. Ten Hoopen and Reuver once again give general expressions for the interspike interval density; however, in their attempt to simplify these expressions, Srinivasan and Rajamannar (1970b) have, in effect, changed the model, and thus their results are inapplicable. Hochman (1971) gives alternate expressions for the general result. When $\varphi(t) = \lambda \exp(-\lambda t)$, the transformed interspike interval density is

$$p^*(s) = \frac{\lambda}{\lambda+s} + \frac{\lambda s}{(\lambda+s)^2} \left\{ \frac{\psi^*(s+\lambda)[\psi^*(s+\lambda) - 1]}{1 - \psi^*(s+\lambda) + \lambda\psi^{*\prime}(s+\lambda)} \right\}, \qquad (5\text{-}4)$$

which closely resembles (4-7).

Ten Hoopen and Reuver suggest that Model II may be of use in modelling Renshaw cells while Model I is of interest in the theory of visual and acoustical contrast-sharpening phenomena.

In a second paper, Srinivasan and Rajamannar (1971), using counter models studied by Ramakrishnan (1954), modify the feedback and feedforward inhibition models and suggest other counter models. Osaki (1971) shows the equivalence of Model I to a two-unit standby redundant model, and proposes additional variations on the models of Srinivasan and Rajamannar.

6. Threshold Models

6.1 Pure Threshold Models

In this paper, we use the term threshold model to refer to neuron models which allow for the temporal summation of excitatory stimuli up to a threshold value such that when the amount of excitation stored in the neuron reaches threshold the neuron discharges.

The simplest threshold model has excitatory stimuli arriving according to a Poisson process with parameter λ, and the neuron fires after the arrival of k stimuli. The waiting time to firing then has a gamma density

$$\frac{\lambda^k t^{k-1} e^{-\lambda t}}{\Gamma(k)}, \quad t > 0. \tag{6-1}$$

We refer to this as a pure threshold model.

6.2 Threshold Models with Decay

Next we can suppose that excitatory stimuli do not have an infinite lifetime. Van der Velden and Bouman (1948), Fortét (1950), Ten Hoopen and Reuver (1965b), and others have proposed a model where the k excitatory stimuli, which are required for the neuron to reach threshold and thus discharge, must all arrive within a period of latent summation, τ. Once the neuron discharges the buildup of excitation begins anew. Exact solutions for the interspike interval distribution in this case are available for k = 2, and for larger values of k for $t < \tau$. For $t > \tau$ an exact solution is extremely difficult. Ten Hoopen and Reuver (1965b) suggest approximating the exact solution using exponentially distributed lifetimes for the excitatory stimuli, with mean τ. Their solution involves finding the roots of polynomials of degree k and k-1. Srinivasan and Rangan (1970) obtain quantities of interest in this problem.

A second model due to Leslie (1969), and interpreted in a neural context by Hochman and Fienberg (1971), has a discharge simultaneously with the k-th

of a group of k excitatory stimuli provided that no time gap between successive stimuli in the group exceeds γ, and no previous stimuli itself occurs simultaneously with a previous discharge. If we set $\tau = k\gamma$, then the solution for the Leslie model, which is a generalization of a discrete model (Leslie, 1967), will give an approximation for the model above. Leslie showed that the L.T. of the interspike interval density for his model, f(t), is

$$f^*(s) = \frac{\Lambda^k E^{k-1}}{1 - \Lambda(1-E)(1 - \Lambda^{k-1}E^{k-1})(1 - \Lambda E)^{-1}} \qquad (6\text{-}2)$$

where

$$\Lambda = \frac{\lambda}{\lambda+s} \quad \text{and} \quad E = 1 - e^{-(\lambda+s)\gamma}. \qquad (6\text{-}3)$$

We can think of γ as a decay parameter, with $(k\gamma)^{-1}$ an approximate average rate of decay. Leslie gives expressions for the mean and variance of the distribution, f(t), e.g. the mean is

$$\frac{1 - (1 - e^{-\lambda\gamma})^k}{\lambda e^{-\lambda\gamma}(1 - e^{-\lambda\gamma})^{k-1}} . \qquad (6\text{-}4)$$

Leslie numerically inverted (6-2) and his graphs show the interspike interval distribution to be unimodal.

We return to extensions of Leslie's model shortly.

6.3 Threshold Models with Inhibition

Ten Hoopen and Reuver (1967b) proposed the following model:

(a) excitatory stimuli arrive according to a renewal process, with p.d.f. $\varphi(t)$;

(b) as soon as k of these excitatory stimuli have arrived the neuron discharges and the summation begins again;

(c) inhibitory stimuli also arrive according to a renewal process, with p.d.f. $\psi(t)$, and which is independent of the excitatory process;

(d) if an inhibitory stimulus arrives in the course of the summation of the excitatory stimuli, all accumulated excitation is wiped out, and summation starts anew.

A variant on this model specifies that an inhibitory stimulus induces a new renewal sequence of excitations, and stops the sequence initiated by the preceding inhibitory stimulus. If the excitation is governed by a Poisson process then the two models are identical; otherwise both models give use to stationary point processes which are non-Markovian non-renewal processes. Ten Hoopen and Reuver (1967b) give expressions for the interspike interval p.d.f. for both models, using many subsidiary functions, but the results are almost impossible to work with in practice.

Srinivasan, Rajamannar and Rangan (1971) obtain further characteristics of the non-Markovian non-renewal processes resulting from the Ten Hoopen and Reuver models. They also consider some extensions, but in all cases their results are essentially at least as complicated as those of Ten Hoopen and Reuver.

Ten Hoopen and Reuver (1967b) claim that, if the incoming stimuli arrive more or less regularly, the p.d.f. for their first model is multimodal. As far as we know, this claim remains unsubstantiated, but it seems quite reasonable given the multimodality in the special case where $k = 1$ (see Section 4).

Osaki and Vasudevan (1972) describe a model similar to the first model of Ten Hoopen and Reuver, with the added feature that on the arrival of an excitatory stimulus the level of excitation in the neuron is increased by an amount x which is a random variable governed by a p.d.f., $\ell(x)$. Above we took $x = 1$ with probability 1. While they give general formulae for the interspike interval density for this model, once again the formulae are of little practical use.

6.4 Threshold Models with Decay and Inhibition

Hochman and Fienberg (1971) have suggested three generalizations of the Leslie model (discussed above in Section 6.2), each of which incorporates inhibitory stimuli. In their Model 1, excitatory (X) and inhibitory (I) stimuli arrive according to independent Poisson processes with parameters λ and μ respectively. The two input processes interact in such a way that a discharge occurs at the k-th X-arrival if and only if:

(a) no two X-arrivals are separated by a time gap greater than γ;

(b) none of the preceding (k-1) X-arrivals itself triggers a discharge;

(c) there is no I-arrival during the chain of k X-arrivals.

Assumptions (a) and (b) are those associated with Leslie's model. The L.T. of $g_1(t)$, the interspike interval p.d.f. for Model 1, is

$$g_1^*(s) = \frac{(s+\mu) f^*(s+\mu)}{s + \mu f^*(s+\mu)} , \tag{6-5}$$

where $f^*(s)$ is given by (6-2), a fact that follows from the renewal equation for $g_1(t)$:

$$g_1(t) = e^{-\mu t} f(t) + \mu \int_0^t Q_o(t-x) g_1(s) dx \tag{6-6}$$

where

$$Q_o(t) = e^{-\mu t} P(t) \tag{6-7}$$

and

$$P'(t) = -f(t). \tag{6-8}$$

$Q_o(t)$ is the probability of no I-arrivals and no discharges in (0,t), while P(t) is the probability of no discharges in (0,t), given no I-arrivals. The mean and variance of the interspike interval distribution can be determined directly from the derivatives of $g_1(t)$, and Hochman and Fienberg give these as

$$m_1 = \frac{1 - f^*(\mu)}{\mu f^*(\mu)} = \frac{[(\lambda+\mu)/\lambda]^k - [1 e^{-(\lambda+\mu)\gamma}]^k}{[1 - e^{-(\lambda+\mu)\gamma}]^{k-1} [\mu + \lambda e^{-(\lambda+\mu)\gamma}]} \tag{6-9}$$

and

$$\sigma_1^2 = \frac{1 + 2\mu f^{*\prime}(\mu) - [f^*(\mu)]^2}{[\mu f^*(\mu)]^2} . \tag{6-10}$$

Setting $\mu = 0$ in (6-9) yields (6-4), the mean for Leslie's model. Fienberg and Hochman (1972) have shown that $g_1(t)$ is unimodal.

Model 2 of Hochman and Fienberg resembles Model 1, but has the added feature that following each I-arrival there is a dead time period during which no arrivals of either type register in the neuron, and this dead-time period is a random variable with p.d.f. $h_2(t)$, and finite mean and variance. The length of the dead-time period is that of a type I counter. The renewal equation for $g_2(t)$, the p.d.f. for the interspike interval distribution under Model 2, is

$$\begin{aligned} g_2(t) &= e^{-\mu t} f(t) + \int_0^t h_2(y) \int_0^{t-y} Q_o(x) \mu g_2(t-y-x)\, dx\, dy \\ &= e^{-\mu t} f(t) + \mu h_2(t) * Q_o(t) * g_2(t), \end{aligned} \tag{6-11}$$

where "*" denotes convolution in (6-11). Taking Laplace transforms yields

$$g_2^*(s) = \frac{(s+\mu) f^*(s+\mu)}{s + \mu[1 - h_2^*(s)] + \mu h_2^*(s) f^*(s+\mu)} . \tag{6-12}$$

Denoting the mean and variance of $h_2(t)$ by m_d and σ_d^2, Hochman and Fienberg express the first two moments of Model 2 in terms of those of Model 1 and of the dead-time distribution, i.e.

$$m_2 = m_1(1 + \mu m_d) \tag{6-13}$$

and

$$\sigma_2^2 = \sigma_1^2(1 + \mu m_d) + \mu(m_1\sigma_d^2 + m_d m_1^2 + m_d^2 m_1) + \mu^2 m_1^2 m_d^2. \tag{6-14}$$

Fienberg and Hochman have shown that $g_2(t)$ can be multimodal. If the dead-time period is of constant length c, then the possible modes of $g_2(t)$ occur approximately at $t = t_Z$, where t_Z is the one mode of $Z(t) = e^{-\mu t} f(t)$, and at

$$t_n = t_z + nc + (n-1)/\mu \quad \text{for } n = 1,2,.... \tag{6-15}$$

Figure 7 (taken from Fienberg and Hochman, 1972) illustrates $g_2(t)$ for $\lambda = 2$, $k = 3$, $\gamma = 3$, $c = 0.5$ and $\mu = 4,5$.

Figure 7 goes about here

In the selective-interaction model of Ten Hoopen and Reuver, where $\varphi(t)$ is a gamma with parameters λ and k, and $\psi(t)$ is an exponential with parameter μ, the distance between the multiple modes depended only on the summation parameter k and the excitation rate λ^{-1}, whereas in Model 2 above the distance between the multiple modes depends only on the dead-time constant c and the inhibition rate μ^{-1}. Thus there are clear physiological grounds for distinguishing between the two models even though they appear to have many of the same characteristics.

Model 3 of Hochman and Fienberg is similar to Model 2, but has the feature that an I-arrival during a dead-time period replaces the residual dead-time period with a new dead-time period. An X-arrival during a dead-time period does not register. If the dead-time period induced by an I-arrival has the p.d.f. $h_3(t)$, then we observe a concatenated dead-time period, $h(t)$, the L.T. of which may be expressed in a way analogous to (6-5):

$$h^*(s) = \frac{(s+\mu)h_3^*(s)}{s + \mu h_3^*(s)} . \tag{6-16}$$

The result is a dead-time period similar to that of one of the models of Coleman and Gastwirth (1969), discussed in Section 4. The L.T. of $g_3(t)$, the interspike interval density of Model 3, is given by replacing $h_2(t)$ by $h^*(t)$ in (6-12), which upon simplification yields

$$g_3^*(s) = \frac{[s + \mu h_3^*(s+\mu)]f^*(s+\mu)}{s + \mu h_3^*(s+\mu)f^*(s+\mu)} . \tag{6-17}$$

The mean and variance of $g_3(t)$ are

$$m_3 = m_1/h_3^*(\mu) \tag{6-18}$$

and

$$\sigma_3^2 = [h_3^{*\prime}(\mu)]\sigma_1^2 + \frac{1 - h_3^*(\mu)}{[h_3^*(\mu)]^2} m_1^2 + \frac{1 - h_3^*(\mu) + \mu h_3^{*\prime}(\mu)}{\mu[h_3^*(\mu)]^2} 2m_1. \tag{6-19}$$

Clearly $m_3 > m_1$, and if $h_2(t) = h_3(t)$ we would expect $m_3 > m_2 > m_1$, as is true when $h_2(t)$ is a gamma density; however, there exist multimodal $h_2(t)$'s for which $m_2 > m_3$. The density $g_3(t)$ is nevertheless always unimodal.

The models above can be made more general by replacing f(t), defined by (6-2), with any p.d.f. which reflects temporal summation of excitation ith decay. Thus, one could use Poisson excitatory arrivals with random amplitudes, a threshold value of say k, and exponential decay, combining the results for this model as given by Karlin (1968), pp. 185-188, and the general results of Osaki and Vasudevan (1972).

Far more difficult to handle mathematically, but perhaps more sensitive from a physiological viewpoint, is a model based on near-Poisson excitatory arrivals, with random amplitudes whose means are functions of the amount of excitation present in the neuron. Then we could consider one version of the model where the means of the random amplitudes are increasing, and another where they are decreasing. A special case of the increasing amplitude version is equivalent, mathematically, to the exponentially decreasing threshold discussed in Section 2. If the excitatory arrivals are non-Poisson, then the discharges will no longer form a renewal process.

Finally, we note a fourth generalization of the Leslie model given by Hochman (1971) in which X-arrivals counteract the effect of previous I-arrivals, shortening the dead-time period and thus "sensitizing" the neuron to future X-arrivals. This model may be used as an extension of either Model 2 or 3

above. We let h(t) be the p.d.f. of the dead-time in the absence of X-arrivals, and $h_4(t)$ be the p.d.f. of the dead-time in their presence. The two p.d.f.'s are related since the dead-time period terminates either due to its natural expiration or due to the m-th X-arrival in the period. Hochman (1971) shows that

$$h_4^*(s) = \left(\frac{\lambda}{\lambda+s}\right)^m + \sum_{n=0}^{m-1} \frac{\lambda^n}{n!}(-1)^n\left[1 - \left(\frac{\lambda}{\lambda+s}\right)^{m-n}\right] \frac{d^n}{ds^n} h^*(s+\lambda). \qquad (6\text{-}20)$$

For m = 1 or m = 2 the resulting interspike interval p.d.f.'s are relatively simple.

The models of this section contain almost all of the "physiological" features of the diffusion models of Section 2; however, by retaining the discrete nature of the inputs and of decay here, we have been able to learn more about the output process of discharges.

7. Refractory Periods

The effect on the p.d.f. of the interspike interval distribution of including a refractory period following a discharge is not at all clear, excepting that we may expect the p.d.f. to shift toward larger intervals. As we mentioned in Section 1, following a discharge the neuron does not respond to any stimulus for a brief period (the absolute refractory period), and then for several seconds thereafter its relative threshold is higher than usual (the relative refractory period). As yet little work has been done to incorporate relative refractory periods into the modelling process except in the diffusion models via the use of exponentially decaying thresholds or barriers, and in simulation studies. In this section we ignore the possibility of relative refractory periods and concentrate on ways to incorporate absolute refractory periods into the models discussed so far.

Let us assume that the length of the absolute refractory period is a random variable with p.d.f. r(t). If all of the input processes to the neuron are Poisson, then the interspike interval p.d.f. is simply r(t)*p(t), the convolution of r(t) with p(t), the interspike interval p.d.f. based on the model without an absolute refractory period. If r(t) is degenerate then the effect of the refractory period is the translation of p(t) to the right. If we allow inhibitory arrivals to interact with the refractory period as has been suggested by Hochman (1971), then calculations are still not too complicated as long as the input processes are Poisson. We note that the calculation of other properties of the output or discharge process, such as the distribution of the number of discharges in an interval of length T, is considerably more difficult, even if we consider a Poisson stream with a fixed dead-time (see Ricciardi and Esposito, 1966; Kabe, 1967; Srinivasan and Vasudevan, 1969).

In the case of non-Poisson input processes, the problem of including a refractory period is more complicated, since following the end of the refractory period we must deal with the interaction-delayed renewal processes. Type I counters are of no use here for the same reason. If the refractory period distribution has a maximum length which is small relative to the mean interspike interval of the process without a refractory period, then it is likely that the effect of the refractory period can be approximated by translating the interspike interval p.d.f. by an amount equal to the mean refractory period (Hochman, 1971).

Models with absolute refractory periods and non-Poisson inputs, and models with relative refractory periods still require considerable attention.

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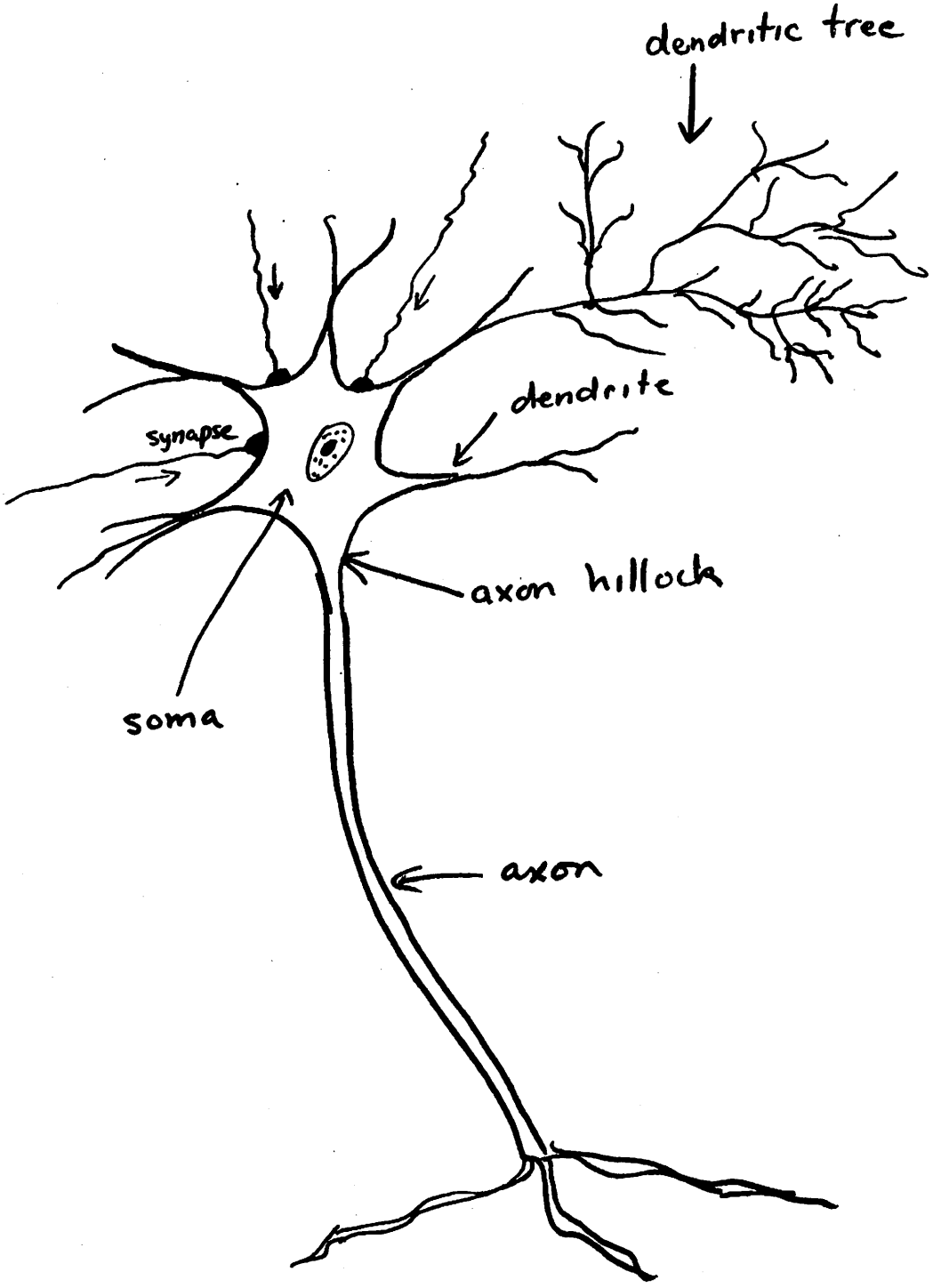

Figure 1.
A typical motor neuron

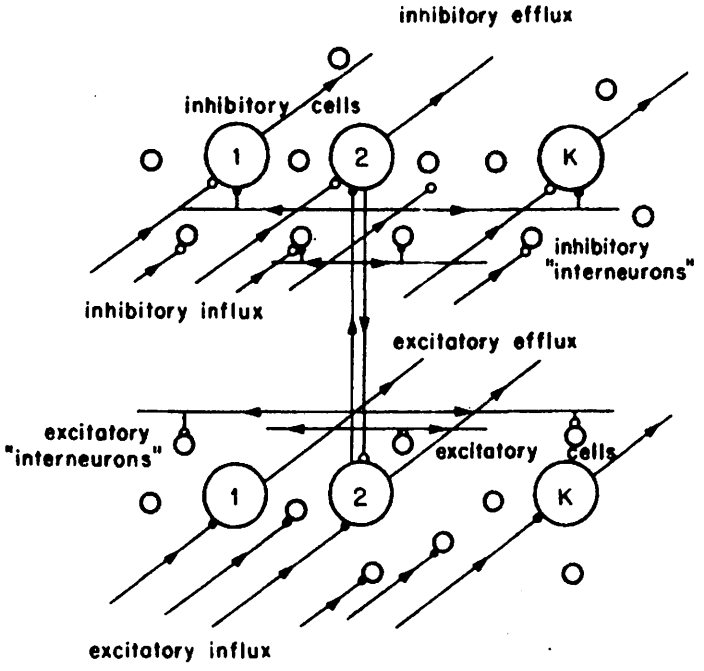

Figure 2.

Interaction of excitatory and inhibitory cells corresponding to neural ensemble studied by Cowan (1970)

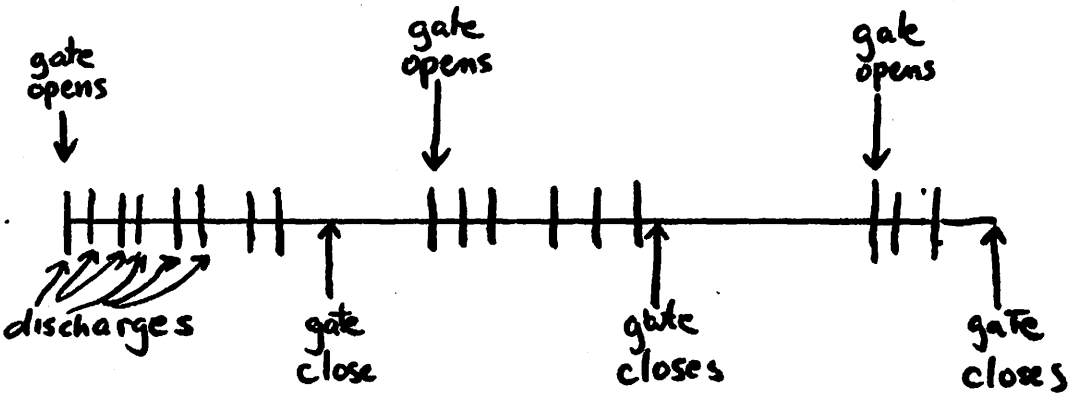

Figure 3.
Typical neural activity as predicted by the model of Smith and Smith (1965).

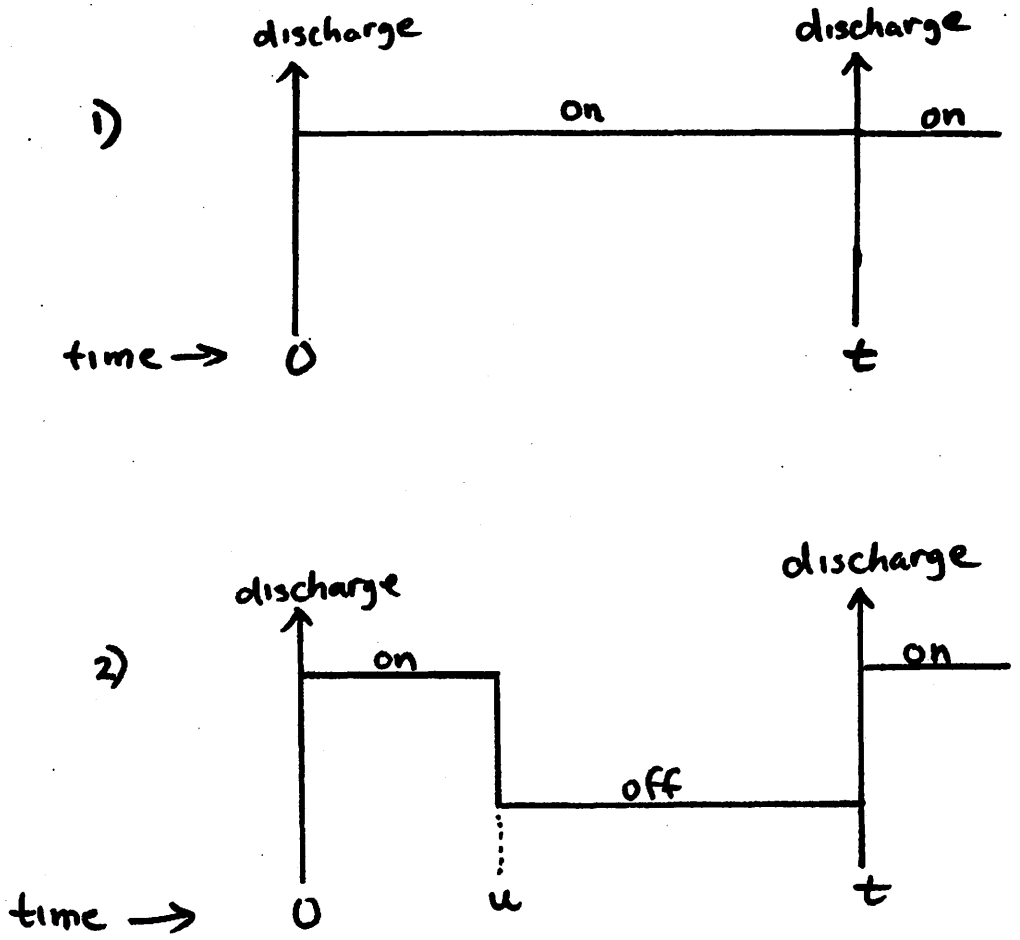

Figure 4.

Two possible setups for an interspike interval in Smith and Smith (1965) model

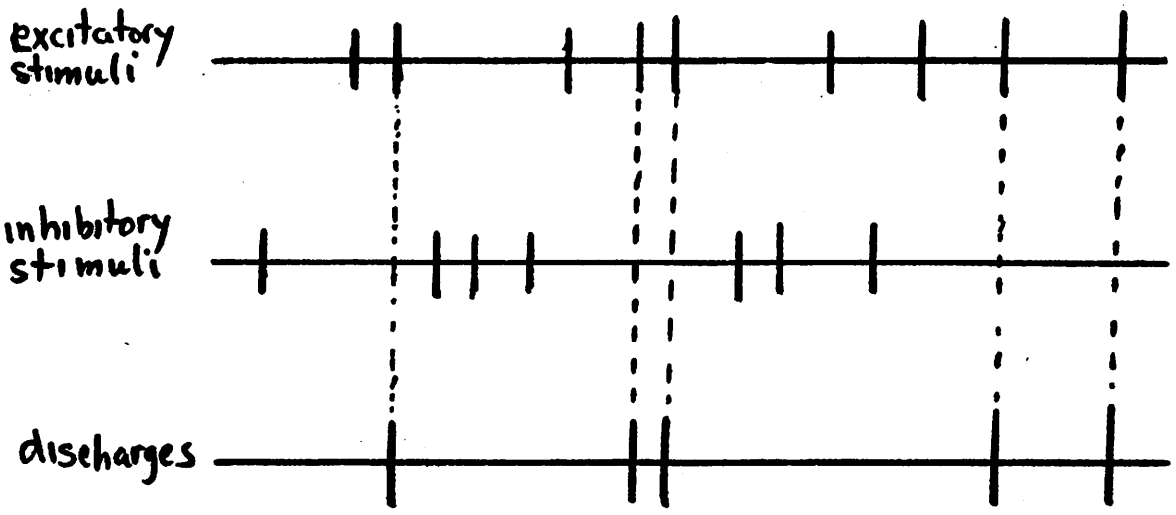

Figure 5

Production of discharges in model of Ten Hoopen and Reuver (1965)

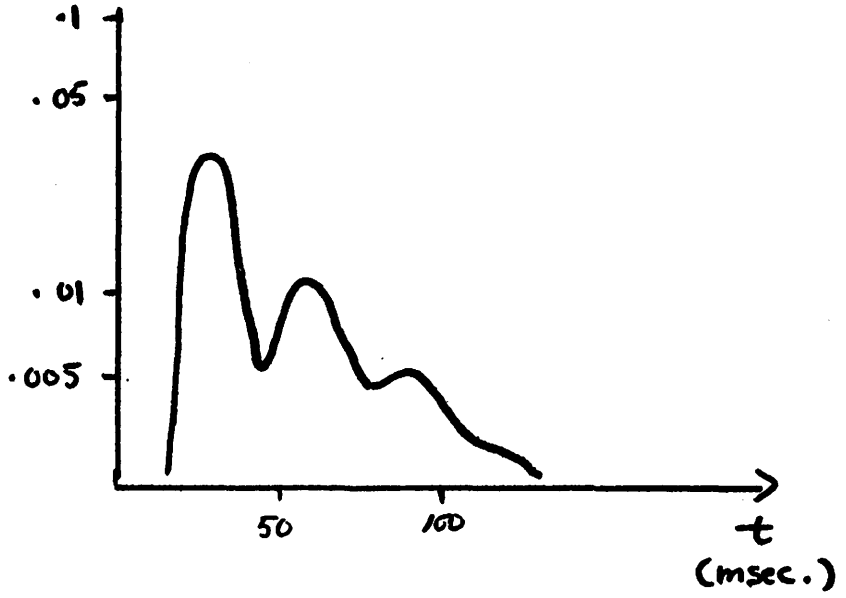

Figure 6

Probability density function, $p(t)$, whose transform is given by (4-2), where $\phi(t)$ is a gamma density with $k=20$ and $\lambda = 0.67$ msec.$^{-1}$, and where $\mu = 0.027$ msec.$^{-1}$

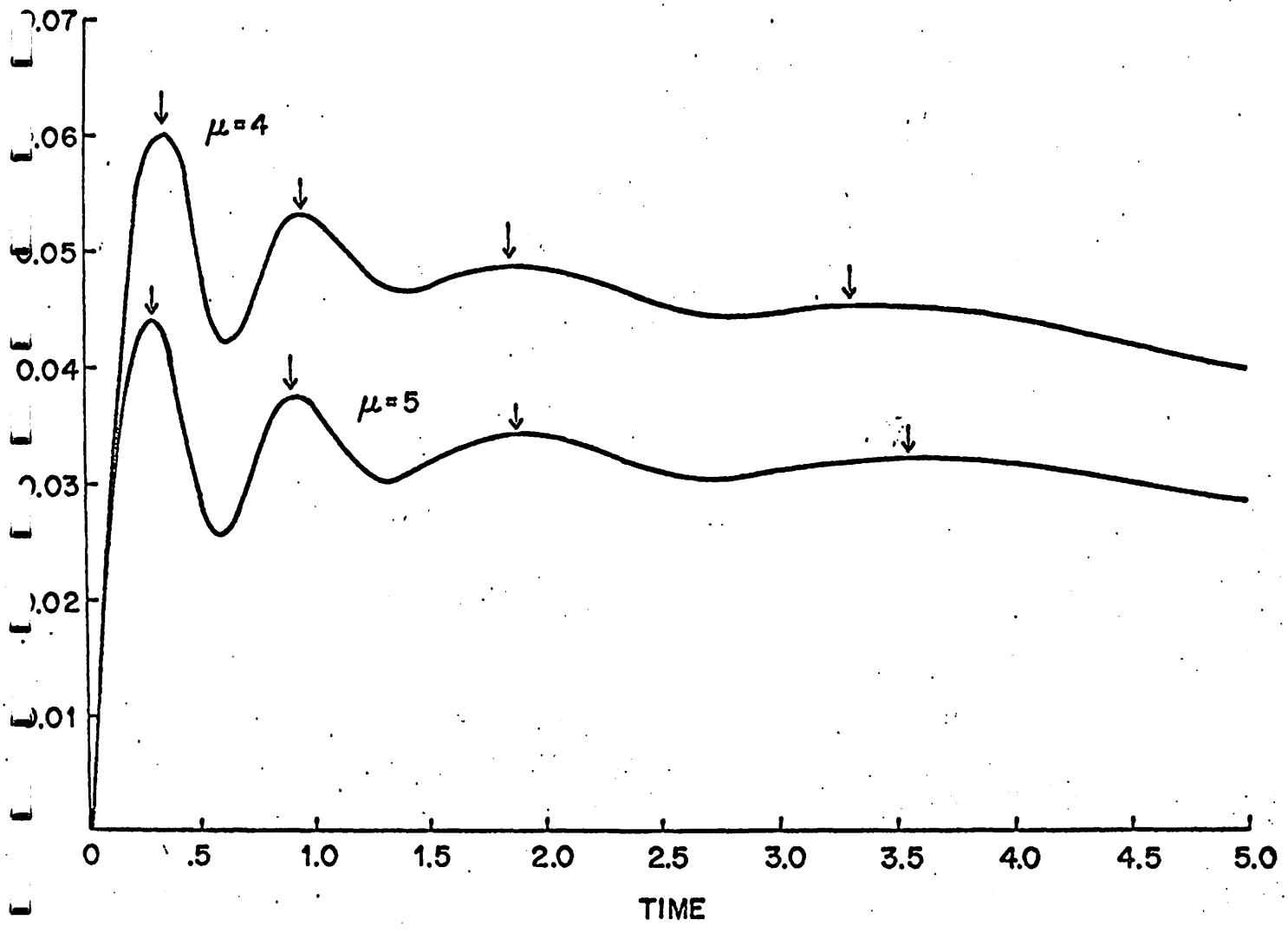

Figure 7

Probability density function $g_2(t)$, whose transform is given by (6-12), with $\lambda=2$, $k=3$ $\gamma=3$, $c=0.5$ and $\mu=4,5$.